Date: 10/10/2020

From: Name
Member ID: XXXX

To: Grievances and Appeals
Anthem Blue Cross and Blue Shield

Re: **ADDITIONAL EVIDENCE FOR URGENT EXPEDITED APPEAL/EXTERNAL REVIEW**

Faxed to: 888-859-3046, 844-521-6940, and 855-607-0518

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Name
Address

October 10, 2020

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Anthem Blue Cross and Blue Shield of Georgia

ADDITIONAL EVIDENCE FOR URGENT EXPEDITED APPEAL/EXTERNAL REVIEW

Dear Sir or Madam:

I am a 43-year-old woman who has been diagnosed with both idiopathic hypersomnia and narcolepsy type 2. These are central primary hypersomnias, chronic neurologic sleep disorders, which are likely to be the same disorder. These are rare diseases characterized mainly by constant overwhelming sleepiness. In addition to that debilitating symptom, I experience excessive overnight sleep, which is disrupted by hundreds of microarousals; sleep inertia; unavoidable daytime sleeping; cognitive dysfunction typical of sleep deprivation, such as attention and memory deficits; and increased pain, which is also thought to be caused by insufficiently restorative sleep.

Since my illness onset in 2010, these symptoms have been almost universally refractory to treatment. There is only one therapy for my rare, disabling, treatment-resistant sleep disorder that has been uniquely helpful for restoring to me some quality of life in the form of improved wakefulness and cognitive function and reduced pain: Xyrem, aka sodium oxybate, a salt of gamma hydroxybutyric acid.

Treatment Failures

Unfortunately, central hypersomnias are notoriously difficult to treat. Since my diagnosis, I have tried numerous therapies with no improvement and with significant side effects.

Before my hypersomnia diagnosis, I tried plaquenil, Cytomel, and Valcyte, all with no improvement. After my hypersomnia diagnosis, I tried numerous stimulating medications, also with no improvement. Both Provigil and Nuvigil led to intolerable headaches and did nothing to improve my symptoms. I am also unable to tolerate Concerta, Adderall, Ritalin, Wellbutrin, or Pitolisant. All caused headaches, tachycardia and elevated blood pressure, and provided no noticeable improvement in my symptoms. Sunosi actually increased both my daytime sleepiness and my cognitive deficits even further.

I've also tried the GABA antagonists flumazenil and clarithromyin. Flumazenil was completely unhelpful, and clarithromycin helped a little for a few months and then never again. Under the care of a neurogeneticist, I even tried some less conventional therapies, including folinic acid, ondansetron, lamotrigine, atomoxetine, and pyridostigmine. Nothing helped, and almost all came with intolerable side effects.

With the desperation of most rare disease patients, I have tried a long list of mostly ineffectual over-the-counter supplements and diets, from a gluten-free diet to vitamin B12 to magnesium, without any whisper of improvement. And lifestyle modifications, such as exercise and maintaining a sleep schedule have also led to zero improvement.

Success With Xyrem

Xyrem is the only medication I have tried that provides me with a significant improvement in my quality of life, and I have been taking it since 2012 without any side effects. It helps to decrease and regulate the number of hours I sleep overnight, and it reduces the sleep inertia I experience. It reduces my sleep disruption and by extension the known multitude of negative long-term health consequences of that sleep disruption, including: body pain/myalgias and the risk of hypertension, dyslipidemia, cardiovascular disease, weight-related issues, diabetes, mood disorders, Alzheimer's disease, stroke, colon cancer, and more.

By the time I started Xyrem, I had become overweight and extremely deconditioned due to spending so much time asleep, with disrupted sleep, and also so much time inactive due to sleepiness/fatigue and pain. I could barely get myself out of bed on my own. After Xyrem, I had enough wakefulness and reduced pain that I could force myself to resume and maintain a regular exercise routine and slowly recondition myself physically.

Nothing I have tried for my hypersomnia has benefited me to the extent that Xyrem has, and it is particularly notable that this benefit occurs without any side effects. I have been on Xyrem since 2012 through numerous insurers, including Anthem BCBS of California and Medicare Part D, until this recent denial.

A Careless Denial

Anthem's denial letters claim that Xyrem is not medically necessary in my case. Contrary to the claims in that denial, the use of Xyrem in my case is supported both by Anthem's medical policy and scientific evidence.

In this appeal, I will show that:

1. Xyrem has been accepted as standard of care for idiopathic hypersomnia, in addition to narcolepsy, for over 10 years by the relevant medical community. The peer-reviewed evidence proves the safety and efficacy of this treatment for cases like mine.
2. This is also demonstrated in the existence of prior precedents where Anthem and other U.S. insurance companies have covered Xyrem for idiopathic hypersomnia. In fact, Anthem has already approved this medication specifically for my case. And I have been approved by numerous other disparate insurance companies, including Medicare Part D, over the past 9 years during which I have been taking Xyrem.
3. The efficacy and medical necessity of Xyrem has been established in my personal case.
4. Since July 2019, Xyrem has had an FDA orphan drug designation specifically for the treatment of idiopathic hypersomnia. Since September 2020, the related Xywav has had an FDA Fast-Track designation for IH.

5. Anthem's "Medical Directors" are clearly unqualified.
6. Anthem Employees are incomptent and nonresponsive.
7. Anthem's policy for off-label medication use clearly indicates need for coverage.
8. Anthem's Xyrem Approval Criteria are outdated, inadequate, and not compatible with medical necessity.
9. Anthem has based its Xyrem approval criteria on diagnostic criteria that are unreliable and meaningless for treatment efficacy: the number of Sleep-Onset REM Periods (SOREMs or SOREMPs) during the Multiple Sleep Latency Test (MSLT). According to extensive peer-reviewed literature, SOREMs do not make any meaningful or reliable distinction between idiopathic hypersomnia and narcolepsy without cataplexy (narcolepsy type 2), for which Xyrem is FDA-indicated. In fact, there is no scientifically-validated test or set of symptoms that can reliably categorize hypersomnolent patients into these two categories. Many experts doubt that these two diagnostic entities represent different diseases at all. SOREMs are an arbitrary basis on which to deny care.
10. Anthem's SOREM-based diagnostic distinction is also systematically discriminatory. The literature clearly shows the MSLT SOREM criteria are biased against recognizing narcolepsy in women, patients diagnosed later in life, and patients who require REM-suppressing medications. I am two of these three. Anthem thus creates a barrier to effective care that operates systematically against patients like me.

In short, I will show that Anthem's denial of my treatment as "not medically necessary" is contrary to their own policies, prior precedent, and established scientific and clinical evidence.

Xyrem represents the only safe and efficacious treatment available to me for a rare, disabling disease. Without Xyrem, I sleep more hours and have increased sleep inertia and severe myalgic pain. Without Xyrem, I have reduced function and quality of life, and significantly elevated risks for a multitude of long-term health problems. Every day without Xyrem, I experience a greater risk to my health and a lower quality of life than if I were being treated appropriately with Xyrem; hence my doctor's enclosed letter requesting "that Anthem BCBS of Georgia approve Xyrem as soon as possible. Further delay of this medically necessary treatment will jeopardize her health. I request that this appeal be considered urgent and be expedited."

Effective treatment is called for in my contract. Xyrem is the one effective treatment to manage my disease.

Anthem, my medical care team, and I all have the same goal—the appropriate treatment and the best outcome for me. Two out of three of us already agree that Xyrem is the only way to achieve that. I believe that Anthem will reach the same conclusion after careful review.

All that I ask is the same consideration, coverage and effective treatment that has been granted to myself previously as well as other Anthem enrollees with narcolepsy type 2 and/or idiopathic hypersomnia who have benefited from this treatment.

I request that Anthem act swiftly to approve my medically necessary treatment with Xyrem, and I look forward to a timely resolution of this matter.

Respectfully,

Name

Enclosures

- Anthem Xyrem approval letter, December 2019
- Physician's letter requesting urgent/expedited approval, October 2020
- Physician's letter of medical necessity, July 2020
- Physician's letter of medical necessity, May 2020
- My patient record from XXX Sleep Center, 2019-2020
- PSG/MSLT, 2011

Abbreviations

- EDS – Excessive Daytime Sleepiness
- ESS – Epworth Sleepiness Scale
- IH – Idiopathic Hypersomnia

- NT1 – Narcolepsy Type 1, aka Narcolepsy With Cataplexy
- NT2 – Narcolepsy Type 2, aka Narcolepsy Without Cataplexy
- OR – Odds Ratio
- MWT – Maintenance of Wakefulness Test
- MSLT – Multiple Sleep Latency Test
- SOREMs or SOREMPs – The Number of Sleep-Onset REM Periods During the MSLT

Incompetent and Nonresponsive Anthem Employees

Since this past May, the month I joined Anthem BCBS of Georgia, I have tried my very best to work with Anthem employees. Unfortunately, they have been almost universally incompetent and nonresponsive.

1. Customer Service doesn't know how to reach the Appeals department.

On 5/7, I called Anthem Member Services to confirm that they had received my prior authorization, which my doctor had submitted on 5/5. Sondra was unable to provide me with any information and transferred me to IngenioRx Home Delivery pharmacy, which was also, unsurprisingly, no help. On 5/18, it took well over an hour on the phone with 3 different Anthem employees (Tishin, Anita, and Kendra) to eventually connect me with the correct Appeals department, IngenioRx. This error was repeated over and over again on numerous subsequent calls.

2. Given incorrect information.

On 5/11, I called Anthem's Pharmacy Member Services. Gloria gave me information from March, which was clearly irrelevant since I'd just joined Anthem BCBS of GA starting in May. She was unable to provide me with any details about my current prior authorization. This error happened repeatedly on subsequent calls with subsequent employees.

3. Informed that Appeal can't be expedited.

On 5/21, Rachel with Anthem's Pharmacy Member Services informed me that my doctor could still request an expedited appeal. My doctor did so, but was then told that this was not possible.

4. Anthem declines to use phone, fax or email.

On 6/18, Alicia with Anthem's Pharmacy Member Services was unable to answer my questions and deferred me to a snail mail letter. She said the use of fax or email was also not possible. Clearly, Anthem has telephones, faxes, and email but declines to use them to help their insured.

5. "Here is my direct phone number and email"... but I won't respond.

On 6/24 I called Anthem Customer Service to request "copies of all documents including…", i.e., the entire contents of my claims file, as per my ERISA rights. I spent nearly an hour on the phone with Jasmine Flournoy, explaining my request and quoting verbatim Anthem's letter describing my rights. However, she was not able to resolve my questions and stated she would call and/or email me back after doing further research. At my request, she also provided me with her direct phone number in case I missed her call. Later that day, she emailed me a single document, which clearly was not "all the documents" I'd requested. I repeatedly emailed her and left her voicemails, but she never responded.

6. Certified Mail and Faxed documents not correctly routed.

Not once, but twice, I've received bizarre, cryptic letters from Anthem. The first, dated 8/8, read as follows:

> We have received your inquiry about the services listed above. Our research indicates the following:
>
> requesting add info like DOS, Claim, Charges, or what action ne
> ed to take.thank you

Needless to say, I had to make several phone calls before finding an employee who could provide any help at all with deciphering this. Melissa Hudson was eventually able to confirm that Anthem had sent this letter in response to a certified letter I'd

sent. However, she could see that my certified letter had not been routed to the correct place, in spite of having been sent with all the correct information to both the correct P.O. Box and the correct fax number. She suggested I fax and email the letter directly to her so she could personally route it correctly. I have no doubt that the second of these bizarre/cryptic letters is also in response to a certified letter that Anthem employees could not correctly route. But, as with Jasmine Fluornoy, Melissa Hudson also will not respond to my repeated emails and voicemails.

Given that Anthem's customer service is near-universally unhelpful, I began to prepare this document.

Xyrem Is Medically Necessary, per Anthem Definition

The Certificate of Coverage for my Anthem plan says that "Anthem considers a service Medically Necessary if it is:"

> - appropriate and consistent with the diagnosis and the omission of which could adversely affect or fail to improve the patient's condition;
> - compatible with the standards of acceptable medical practice in the United States;
> - not provided solely for your convenience or the convenience of the Doctor, health care provider or Hospital;
> - not primarily Custodial Care;
> - provided in a safe and appropriate setting given the nature of the diagnosis and the severity of the symptoms. For example, a Hospital stay is necessary when treatment cannot be safely provided on an outpatient basis; and
> - cost-effective compared to alternative interventions, including no intervention. Cost effective does not always mean lowest cost. It does mean that as to the diagnosis or treatment of the Member's illness, injury or disease, the service is: (1) not more costly than an alternative service or sequence of services that is medically appropriate, or (2) the service is performed in the least costly setting that is medically appropriate.

As I will show in detail, Xyrem is appropriate for the treatment of both narcolepsy and idiopathic hypersomnia, and its omission does significantly adversely affect my condition. Xyrem is clearly accepted as standard of care in the U.S. It is absolutely not provided solely for my or my doctor's convenience. It is actually quite inconvenient for both of us to access, and it is inconvenient for me to take. However, it is worth it because of the significant health benefits. Xyrem has nothing to do with custodial care

and it is provided easily at home. There is no alternative medication, with the exception of Xywav, which has just been approved by the FDA.

Anthem Policy Requires Coverage for Narcolepsy

Anthem's Approval Criteria for Xyrem clearly require coverage for both narcolepsy type 1 and type 2, with which I have been diagnosed. I have repeatedly provided Anthem with this information, via letters and medical records from my expert sleep specialist. And Anthem has clearly confirmed receipt of these letters. However, the anonymous reviewers continue to say that they "did not receive or did not see certain information."

Additionally, Anthem's initial anonymous "Medical Director Decision" provides only an extremely brief and insufficient "Internal MD Rationale: Records reviewed; 43 yo w/ h/o Idiopathic Hypersomnia, Migraines, on Xyrem, denial upheld." The only "record" found in the "claims file" Anthem sent to me is a single office visit note from my November 2019 visit with Dr. X. I am left to conclude that the reviewers did not read or consider any of the provided medical records, doctor's letters, etc.

Regardless, Anthem's reviewers are not qualified to comment on the medical necessity of Xyrem. One is an internal medicine doctor, and one is a neurologist. Neither is a sleep specialist. Given that narcolepsy and idiopathic hypersomnia are both rare diseases, even many sleep medicine specialists have very limited experience with, and knowledge of, these complex disorders and their appropriate treatments.

Narcolepsy Type 2 and IH Are the Same Disorder

As I will show in detail, the diagnostic differentiation of NT2 and IH based on SOREMs has been repeatedly shown to be completely inadequate. Furthermore, data-driven cluster analysis has shown that patients with NT2 and IH are sorted statistically into the same cluster—with the implication that the diseases are similar enough that they cannot be reliably distinguished on clinical grounds either.

> Cluster analysis confirmed that narcolepsy type 1 and polysymptomatic hypersomnia are independent sleep disorders. People who were initially diagnosed with Nw/oC [narcolepsy without

> cataplexy; NT2] and IHw/oLST [IH without long sleep time] formed a single cluster, referred to as "combined monosymptomatic hypersomnia/narcolepsy type 2."
>
> (*Sonka K et al, Sleep Medicine, 2015: 16(2):225-31*).

This is exactly the cluster in which my disease falls, where NT2 and IH are indistinguishable clinically, as well as diagnostically.

Anthem's Off-Label Drug Policy Requires Coverage for Chronic and Disabling Conditions

Anthem's denial directly contravenes its own policy for off-label drugs. The Anthem Blue Open Access POS Certificate of Coverage for Revel Systems, Inc. explicitly states that off-label drugs are required for Members with disabling conditions:

> When prescribed to a Member with a life-threatening or chronic and disabling condition or disease, benefits are provided for the following:
>
> - Off-label Drugs
> - Medically Necessary services associated with the administration of such a drug.
>
> An off-label drug is a drug prescribed for a use that is different from the use for which it was originally approved for marketing by the federal Food and Drug Administration.

I am disabled by my chronic neurologic sleep disorder. I have been receiving disability benefits from the Social Security Administration as well as both of my private disability insurers (CIGNA/LINA and Principal) since 2012. Thus, Xyrem is clearly defined as medically necessary for my condition under this policy.

Anthem's Xyrem Approval Criteria Are Outdated, Inadequate, and Not Compatible With Medical Necessity

Anthem's criteria are based on a scant eight references. A quick examination reveals these to be irrelevant, inadequate, and/or outdated for addressing the use of Xyrem for IH and/or NT2:

- Epstein LJ, Kristo D, Strollo PJ, et al. Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults: Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2009; 5(3):263-276. Available

from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2699173/pdf/jcsm.5.3.263.pdf. Accessed March 8, 2019.

- Kapur VK, Auckley DH, Chowdhri S, et.al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: An American Academy of Sleep Medicine clinical practice guideline. *J Clin Sleep Med.* 2017; 13(3): 479-504. Available from: https://aasm.org/resources/clinicalguidelines/diagnostic-testing-osa.pdf. Accessed April 8, 2019.

Irrelevant. These two references are for obstructive sleep apnea (OSA) and say nothing about appropriate treatments for central hypersomnias. The first says only that one should carefully evaluate for narcolepsy and other sleep disorders if the patient's sleepiness does not improve with treatment of OSA. The second says only that HSAT (home sleep apnea testing) should not be used in a clinically-complicated patient population (e.g., one with other potential sleep disorders, such as narcolepsy). These references are clearly completely irrelevant to the treatment of central hypersomnias with Xyrem. Perhaps they were included as references for the use of ESS and MWT for monitoring sleepiness. However, these tools are inadequate and inappropriate for central hypersomnias, as I will show.

- Sateia MJ. International classification of sleep disorders – third edition: Highlights and modifications. *Chest.* 2014 Nov; 146(5): 1387-1394.

Inadequate. Since this does not contain any data or recommendations for therapies, it is presumably included simply for its much-criticized and invalidated diagnostic criteria for the central hypersomnias. I have provided extensive evidence that the MSLT SOREM criteria from the ISCD-3 are invalidated, unreliable, and discriminatory.

- Wise MS, Arand DL, Auger RR, Brooks SN, Watson NF; American Academy of Sleep Medicine. Treatment of Narcolepsy and other Hypersomnias of Central Origin. Sleep. 2007 Dec 1;30(12):1712-27. Available from: http://www.aasmnet.org/Resources/PracticeParameters/Review_Narcolepsy.pdf. Accessed March 8, 2019.

Inadequate and outdated. This practice recommendation, which does not mention the use of Xyrem for IH, is well over a decade old. One can practically hear it creaking when it cites a 1988 study as evidence for modafinil. Anthem ignores numerous more recent reviews and recommendations that include the recommendation of Xyrem for treatment-refractory IH.

- DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: March 8, 2019.

Inadequate. The Xyrem package insert by legal definition can only include information related to on-label uses.

- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2019. URL: http://www.clinicalpharmacology.com. Updated periodically.
- DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
- Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2018; Updated periodically.

Inadequate and Outdated. A 2019 study has confirmed long-standing physician complaints that commercially-supplied drug compendia are frequently inconsistent with each other, outdated, and incomplete, especially for rare disease indications. Less than a third of a cross-sectional sample of 273 established treatments were included in either compendia, and roughly half of the diseases examined had 1 or fewer treatment options (e.g., 45% in DRUGDEX; 68% in AHFS). The authors conclude:

> These shortcomings mean that patients with rare but treatable diseases may not be able to access necessary, evidence-based therapies when these compendia are used to make coverage determinations… Policies to reduce the reliance on these compendia for coverage determinations should be developed… It is likely that there must always be an option to use supplementary evidence to support necessary treatments for patients with rare diseases and special conditions.
>
> (Barbieri et al. 2019)

I investigated the AHFS coverage of Xyrem and found that it is clearly outdated. For example, it states, “Not known whether distributed into milk; caution advised.” However, there are several studies indicating that Xyrem is distributed in milk, but that due to its short half-life, one may still breastfeed with certain caveats. For example:

> The GHB concentration found in breast milk followed the same pattern as for the blood, with the highest concentration being 23.19mg/L, 1h after sodium oxybate administration and the lowest 0.99mg/L, 5h after the medication's intake.
>
> (Busardò FP, Bertol E, Mannocchi G, et al. Determination of GHB levels in breast milk and correlation with blood concentrations. Forensic Sci Int. 2016;265:172–81.)

Additionally, the newest reference in the AHFS document is from 2012, and the majority are from 2002. And Lexicomp refers to clinical practice guidelines from 2007, which are well over a decade old.

Outdated and inadequate references lead to outdated and inadequate Approval Criteria, which are not compatible with the current standard of care. Anthem's Xyrem Approval Criteria still require SOREMs for diagnosis of NT2, while the consensus of current medical literature clearly indicates that this is inaccurate and discriminatory, as I will show. Anthem's Approval Criteria require improvement in ESS or MWT; however these tests measure only sleep propensity and are completely inadequate to appropriately measure improvements in hypersomnia symptoms.

In summary, Anthem's Xyrem Approval Criteria are outdated, inadequate, and not compatible with Anthem's own definition of medical necessity. I expect that Anthem will correct the oversight this has created in my case, by swiftly approving my coverage for Xyrem.

Precedents for Xyrem for the Treatment of Idiopathic Hypersomnia

I have been personally approved for and successfully treated with Xyrem since 2012, via numerous insurers, including Anthem BCBS of California and ExpressScripts Medicare Part D. I provide the details in the table below, along with precedents from numerous other patients with IH who have graciously shared their coverage information with me via hypersomnia support groups, so that I may continue to be covered for the same successful treatment with Xyrem.

These insurers understand that there is no benefit in denying access to the most effective drug for a given individual with a rare, poorly-understood disease who requires individualized treatment. They recognize that the clinical standard of care for idiopathic hypersomnia is the same as that for narcolepsy type 2 and includes sodium oxybate, especially as an option for patients who have treatment-refractory hypersomnia.

All that I ask is the same treatment that Anthem has granted to me personally and other subscribers like X, and that health insurers across the board are appropriately granting to their insured, as per the following table.

Table 1: Precedent for Insurance Approval for Xyrem to Treat Idiopathic Hypersomnia

IH Patient or Patient Guardian	**Insurance Provider**	**Prescribing Doctor**	**Treatment First Approved**
Myself*	Anthem BCBS of CA	Dr. Lynn Marie Trotti	2019
Myself*	ExpressScripts Medicare Part D	Dr. Lynn Marie Trotti	2019
Myself*	Aetna Employer Plan for Company A	Dr. Lynn Marie Trotti	2016
Myself*	Cigna Employer Plan for Company B	Dr. Lynn Marie Trotti	2016
Myself*	Cigna Healthcare Individual Plan	Dr. Lynn Marie Trotti	2014
Myself*	Cigna Employer Plan for Company C	Dr. Gazala Quraishi	2012
X	Anthem (Virginia)	Dr. Douglas Puryear	2020
Y	North Carolina Medicaid	Dr. Steve Thomas Kirk	2018
Z*	BC/BS of Alabama	Dr. James Roy	2009
Z*	Humana Employers Health Plan of GA	Dr. Lynn Marie Trotti	2014
A*	Cigna HealthCare of North Carolina	Dr. Jeannie Gingras	2019
A*	BC/BS of NC	Dr. Jeannie Gingras	2020
B*	MDwise	Dr. Yuzhu Tang	2017
B*	Aetna	Dr. James T. Fesenmeier	2018
C	United HealthCare of Arizona	Dr. Paul Barnard	2017
D	Virginia Premier	Dr. Neil Crowe	2018

E	Group Health Incorporated (EmblemHealth)	Dr. Michael Thorpy	2016
F	Aetna (Washington state)	Dr. Oneil S. Bains	2019
G	United Health Care (Anthem)	Dr. Charu Sabharwal	2019
H	United Healthcare Empire Plan	Dr. Dorian Gomez	2020

*Patient was approved for Xyrem treatment under multiple insurers on separate occasions.

The Evidence for Xyrem

Xyrem Has Demonstrated Efficacy for This Patient

Significant Improvement in Multiple Symptoms

I have been on Xyrem since 2012 because it is the only medication out of the numerous medications I've tried for my neurologic sleep disorder that provides me with a significant improvement in my symptoms and quality of life. When I had to stop Xyrem this past Spring after Anthem denied my coverage, I was quickly plunged into a torture of worsened EDS and cognitive dysfunction; longer/more disrupted overnight sleep; increased sleep inertia; and increased physical pain.

My symptomatic improvements with Xyrem are not well-captured by either the ESS or the MWT, and this is true in general for people with central hypersomnias. The ESS is not an appropriate test for measuring our symptomatic improvement.

> Abuse can be defined as "Improper use or handling" or "An unjust or wrongful practice."[1] By either of these definitions, the Epworth Sleepiness Scale (ESS)[2] is being abused. How and by whom you may ask? The answer, insurance companies and their surrogates, and we, sleep clinicians, are complicit in these activities... one could surmise that the ESS is the metric by which the insurer assesses whether or not the patient is sleepy. If this is true, it is a prime example of using a tool for a purpose for which it was not intended... For this purpose, it is actually a poor instrument.
>
> (Quan, Stuart F. "Abuse of the Epworth Sleepiness Scale." *Journal of Clinical Sleep Medicine*, vol. 09, no. 10, 2013, pp. 987–987., doi:10.5664/jcsm.3062.)

Although Xyrem improves all the symptoms I've listed above, I continue to require 2 daytime sleep sessions. Therefore, when I complete the ESS questionnaire, I answer it as if I were in the sleepiest phase of my day. The ESS is simply not sensitive for the nuances of a disease in which sleepiness fluctuates significantly throughout each day.

Like the ESS, the MWT only measures sleep propensity—and nothing else (Johns, Murray W. 2000). As my sleep doctor noted, performing an MWT in an attempt to further document improvement with Xyrem, during the ongoing COVID-19 pandemic, would expose me to unacceptable risk, especially given that we already know I experience significant clinical improvements with Xyrem. Furthermore, since the MWT is only a measure of the propensity to fall asleep, it is therefore inadequate to determine symptomatic improvement in hypersomnias. It fails to capture numerous aspects of the experience of excessive daytime sleepiness, including brain fog, cognitive dysfunction, etc., which contribute substantially to my disease burden and functional limitations. It also fails to capture the reductions in long-term risk due to disrupted sleep.

Xyrem Corrects Disrupted Sleep

I am not surprised that Xyrem has been the only effective treatment for me. There are particular features of my case that logically make Xyrem more likely to help: namely, the abnormal features of my nighttime sleep, which are all perfect matches to the ways in which Xyrem affects sleep.

The supposedly "typical" description of IH sleep includes a very high sleep efficiency, few arousals, insensibility to noise or other disturbances, a high slow-wave sleep percentage ("deep sleep"), and normal REM. My sleep is the opposite of this profile and much more like NT2, hence my dual diagnosis, as detailed by my sleep specialist in her letters.

Aside from my lack of SOREMs, my sleep is characteristic of a "typical" narcolepsy patient. According to my sleep study report:

> Sleep efficiency was normal at 91.1%, with a latency to sleep of 5.0 minutes. The total arousal index was elevated at 42.0 arousals/hour due to spontaneous arousals. Distribution of sleep stages was notable for an increased percentage of stage 2 sleep, and a decreased percentage of slow wave sleep. Sleep architecture was fragmented. The REM latency was reduced at 69.5

> minutes. A reduced REM latency can be seen in narcolepsy, depression, or prior REM deprivation.

My arousal index of 42 per hour indicates that I am waking up nearly every minute, although I only notice waking up about once per hour. I sleep shallowly and have never slept through an alarm. My slow-wave sleep percentage was only 5.5% of the TST (total sleep time), which is significantly less than the typical 10-20% for adults. My sleep stage progression is highly disordered.

Xyrem promotes peaceful, uninterrupted sleep. Of particular benefit to me, it increases the slow-wave sleep I lack, and it is one of only a few drugs known to do so. On Xyrem, I sleep through the night without interruption, other than to take my second dose. Additionally, my slow-wave sleep is increased dramatically, according to the at-home single-channel EEG device I use to monitor my sleep. In other words, Xyrem normalizes my sleep. This is especially important given the known negative health effects of disrupted sleep.

Disrupted Sleep Leads to Multiple Serious Long-Term Health Consequences

Executive Summary

Disrupted sleep, specifically including reduced slow wave sleep (SWS), is a serious problem. It immediately leads to impaired daytime function, including cognitive, memory and performance deficits; and it eventually leads to a significantly increased risk for Alzheimer's disease. Disrupted sleep has also been shown to immediately cause increased stress responsivity, somatic pain, emotional distress and mood disorders. Long term, it significantly increases risk for heart attacks, strokes, cancer, and more. Clearly, it is of paramount importance to reduce sleep disruption as swiftly and completely as possible, hence my doctor's enclosed letter requesting "that Anthem BCBS of Georgia approve Xyrem as soon as possible. Further delay of this medically necessary treatment will jeopardize her health. I request that this appeal be considered urgent and be expedited."

Negative Effects of Reduced Slow Wave Sleep

Disrupted/reduced SWS and slow wave activity (SWA) have been shown to increase sleep fragmentation, increase sleep propensity, and impair daytime function. Increasing SWS can improve daytime function in patients with nonrestorative sleep.

> SWS is precisely regulated and compensated for. The dominance of SWS in frontal areas associated with higher brain function, or in areas that have been very active during wakefulness, emphasizes the significant role of SWS. The negative correlations between SWA and SWS and measures of sleep continuity in animals and humans suggest that SWS contributes to sleep continuity. Experimental disruption of SWS increases shallow sleep and sleep fragmentation, increases daytime sleep propensity, and may impair daytime function... pharmacologic enhancement of SWS may lead to improvements of sleep maintenance and daytime function in patients with primary insomnia or nonrestorative sleep.
>
> (Dijk, Derk-Jan. "Regulation and Functional Correlates of Slow Wave Sleep." *Journal of Clinical Sleep Medicine*, vol. 5, no. 2 suppl, 2009, doi:10.5664/jcsm.5.2s.s6.)

Reduced SWA leads to cognitive and memory deficits.

> Even modest sleep restriction, especially the loss of sleep slow wave activity (SWA), is invariably associated with slower electroencephalogram (EEG) activity during wake, the occurrence of local sleep in an otherwise awake brain, and impaired performance due to cognitive and memory deficits. Recent studies not only confirm the beneficial role of sleep in memory consolidation, but also point to a specific role for sleep slow waves. Thus, the implementation of methods to enhance sleep slow waves without unwanted arousals or lightening of sleep could have significant practical implications.
>
> (Bellesi, Michele, et al. "Enhancement of Sleep Slow Waves: Underlying Mechanisms and Practical Consequences." *Frontiers in Systems Neuroscience*, vol. 8, 2014, doi:10.3389/fnsys.2014.00208.)

Thus, my significantly reduced slow wave sleep of 5% (compared to the 10-20% norm) is a significant problem for my health. But this problem is clearly corrected by Xyrem, which increases my SWS to greater than 20%.

Sleep Disruption Is a Causal and Instigating Factor for Alzheimer's Disease

Alzheimer's disease (AD) is a terrifying prospect for everyone as they age. It's even more terrifying for patients with sleep disorders, because it's much more likely to occur. Thankfully, treating sleep disorders, with a goal to improve restorative sleep,

can significantly delay the onset of cognitive decline. This is therefore an extremely important reason to treat hypersomnias with disrupted sleep appropriately and swiftly with Xyrem.

> The preclinical stage of AD is characterized by β-amyloid (Aβ) aggregation into amyloid plaques and tau phosphorylation and aggregation into neurofibrillary tangles. There is a consensus on the importance of sleep within this context: the bidirectional relationship between sleep and AD pathology is supported by growing evidence that proved that the occurrence of sleep changes starting from the preclinical stage of AD, many years before the onset of cognitive decline.
>
> (Cordone, Susanna, et al. “Sleep and β-Amyloid Deposition in Alzheimer Disease: Insights on Mechanisms and Possible Innovative Treatments.” *Frontiers in Pharmacology*, vol. 10, 2019, doi:10.3389/fphar.2019.00695.)

> Until recently, sleep disruption was thought of as a symptom of neurodegenerative disease. Now, however, an increasing number of studies indicate that sleep disruption may be a causal and instigating factor linked to the pathophysiology of Alzheimer's disease. Deficient and poor quality sleep, along with several sleep disorders, predict an increased risk of cognitive decline and the conversion to MCI and Alzheimer's disease. Sleep impairments precede the onset of such clinical outcomes by years if not decades. Conversely, treating sleep disorders such as sleep apnoea can delay the onset of cognitive decline by almost a decade (Mander *et al.*, 2016; Musiek and Holtzman, 2016).
>
> (“A Restless Night Makes for a Rising Tide of Amyloid.” *Medscape*, 29 Sept. 2017, www.medscape.com/viewarticle/884723.)

Sleep Disruption Leads to Negative Health Outcomes

In addition to worsening daytime function and sleepiness, as well as worsening current and future cognitive function, sleep disruption has many other negative consequences. These include increased somatic pain, mood disorders, cardiometabolic disorders, stroke, and cancer. The extreme importance of reducing sleep disruption cannot be overstated.

> Sleep disruptions have substantial adverse short- and long-term health consequences... Sleep disruption is associated with increased activity of the sympathetic nervous system and hypothalamic–pituitary–adrenal axis, metabolic effects, changes in circadian rhythms, and proinflammatory responses. In otherwise healthy adults, short-term consequences of sleep disruption include increased stress responsivity, somatic pain, reduced quality of life, emotional distress and mood disorders, and cognitive, memory, and performance deficits... Long-term consequences of sleep disruption in otherwise healthy individuals include hypertension, dyslipidemia, cardiovascular disease, weight-related issues, metabolic syndrome, type 2 diabetes mellitus, and colorectal cancer.

(Medic, Goran, et al. “Short- and Long-Term Health Consequences of Sleep Disruption.” *Nature and Science of Sleep*, Volume 9, 2017, pp. 151–161., doi:10.2147/nss.s134864.)

The cumulative long-term effects of sleep loss and sleep disorders have been associated with a wide range of deleterious health consequences including an increased risk of hypertension, diabetes, obesity, depression, heart attack, and stroke. After decades of research, the case can be confidently made that sleep loss and sleep disorders have profound and widespread effects on human health.

(Colten, Harvey R., and Bruce M. Altevogt. *Sleep Disorders and Sleep Deprivation: an Unmet Public Health Problem*. Institute of Medicine, 2006.)

Xyrem Is the Standard of Care in the Scientific Literature & Clinical Community

Executive Summary

Xyrem is clearly included in the clinical standard of care for treatment-refractory idiopathic hypersomnia. Sodium oxybate has a documented history of use for the treatment of non-cataplectic hypersomnias of more than two decades. Xyrem was first FDA-approved for use in narcolepsy in 2002, and the peer-reviewed literature documents clinicians using it to treat idiopathic hypersomnia shortly thereafter (Ali et al. 2009). Numerous current literature reviews, practice guides, consensus statements, and clinical decision support tools confirm the recommendation of sodium oxybate for treatment-refractory idiopathic hypersomnia.

Current reviews and recommendations for the treatment of idiopathic hypersomnia consistently emphasize two important points:

1. IH requires carefully individualized treatment for each patient, because of the extreme variability seen in symptoms and treatment responses.
2. Xyrem is part of the clinically-accepted standard of care of treatment-refractory hypersomnia.

Major Consensus Treatment Guidelines

France's consensus treatment guidelines for the hypersomnias were updated in 2017, a decade more recent than the outdated Wise et al AASM guidelines from 2007 that are used by Anthem:

> The choice of treatment for IH patients resistant to modafinil and to methylphenidate requires the collective advice of the Narcolepsy-Hypersomnia Reference Centre….Recommendations: Sodium oxybate can be effective on EDS and sleep inertia in IH.
>
> (Lopez, R et al. 2017. "French Consensus. Management of Patients with Hypersomnia: Which Strategy?" *Revue Neurologique* 173(1–2): 8–18.)

Of special note in the French consensus, the level of evidence for use of Xyrem is graded identically to the level of evidence for the use of dextroamphetamine—a drug widely used as a first- or second-line treatment strategy for IH.

Other Representative Literature Reviews and Practice Guides

> Studies illustrate the respective benefit of modafinil, sodium oxybate, pitolisant, mazindol, flumazenil, and clarithromycin in IH treatment.
>
> (Arnulf, Isabelle, Smaranda Leu-Semenescu, and Pauline Dodet. 2019. "Precision Medicine for Idiopathic Hypersomnia." Sleep Medicine Clinics 14(3): 333–50.)

> Unlike modafinil and psychostimulants, [sodium oxybate] is not considered first or second line for IH treatment, but may be considered in individual, treatment-refractory cases.
>
> (Saini, Prabhjyot, and David B. Rye. 2017. "Hypersomnia: Evaluation, Treatment, and Social and Economic Aspects." *Sleep Medicine Clinics* 12(1): 47–60.)

> Treatment options for treatment-refractory IH [include] sodium oxybate, titrated up to 4.5 g twice nightly (separated by 2.5–4.0 h); mean dose in IH patients 4.3 g/night; lower than in patients with NT1
>
> (Trotti, Lynn Marie. 2017. "Idiopathic Hypersomnia." Sleep Medicine Clinics 12(3): 331–44.)

> Treatment for [non-cataplectic] hypersomnolence may have to be more aggressive (high-dose stimulants, sodium oxybate, etc.) on a case-by-case, empirical trial basis….

> Sodium oxybate can help significantly, notably if sleep difficulties are present.
>
> (Mignot, Emmanuel J.M. 2012. “A Practical Guide to the Therapy of Narcolepsy and Hypersomnia Syndromes.” Neurotherapeutics 9(4): 739–52.)

Clinical Decision Support Tools

The literature I have cited is not obscure. The same recommendations are incorporated in the major evidence-based point-of-care tools, Dynamed and UpToDate. They reflect that same literature consensus, indicating the use of sodium oxybate as a therapy for IH in treatment-refractory cases.

UpToDate, similar to the French consensus, specifically treats sodium oxybate and amphetamines as second-line therapies which can be tried if treatment with modafinil fails. (Chervin, Ronald D. 2020. “Idiopathic Hypersomnia.” In *UpToDate*, eds. Thomas E Scammell and April F Eichler. Waltham, MA: UpToDate)

> Treatment [for idiopathic hypersomnia] may include modafinil, armodafinil, methylphenidate, amphetamines, sodium oxybate, clarithromycin, flumazenil, or pitolisant….
>
> Sodium oxybate may be considered in individual, treatment-refractory cases - consider dosing as in treatment for narcolepsy.
>
> (DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. T921449, Central Disorders of Hypersomnolence; [updated 2018 Nov 30, accessed 2020 Sep 4].)

Benefits for IH Are Unique to Xyrem

For IH patients who benefit from Xyrem, the effects are downright astonishing. The most important study released to date on Xyrem for IH compared 49 patients with either IH or NT1 using sodium oxybate. It found that Xyrem is just as effective for daytime sleepiness in IH as it is in NT1, even in patients who were refractory to stimulants. In addition, it found that Xyrem provides other major benefits to IH patients unique to this treatment, especially the reduction in disabling sleep inertia.

> The drug improved daytime sleepiness to the same degree as in patients with narcolepsy type 1. This improvement was observed despite the fact that SXB [sodium oxybate] was used at a lower dose in IH than in NT1 and after patients had tried other stimulants.

> In addition, the treatment reduced the severe morning inertia, facilitated sleep onset at night, and shortened the prolonged nighttime sleep of patients with IH.
>
> A prominent result here is the clear benefit of SXB treatment on severe sleep inertia in patients with IH. The drug improved severe sleep inertia in 71% of the hypersomnia patients.
>
> Severe sleep inertia is one of the most disabling symptoms in IH. To date, no [other] drug has been shown to specifically improve this symptom.
>
> (Leu-Semenescu, Smaranda, Pauline Louis, and Isabelle Arnulf. 2016. "Benefits and Risk of Sodium Oxybate in Idiopathic Hypersomnia versus Narcolepsy Type 1: A Chart Review." *Sleep Medicine* 17: 38–44.)

Xyrem Has an FDA Orphan Designation for IH, and Xywav Has Fast-Track Designation

Since July 2019, Xyrem has had an FDA orphan drug designation specifically for the treatment of IH. In September 2020, the related Xywav was granted a Fast-Track designation by the FDA for the treatment of IH. These are the only FDA-approved formulations of GHB currently available. Clearly, the FDA is aware that this group of medications is effective for IH.

The relevant record for orphan designation from the FDA website is shown in the Figure below and may be viewed online.

U.S. Department of Health & Human Services

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Generic Name:	Gamma-hydroxybutyric acid
Date Designated:	07/31/2019
Orphan Designation:	Treatment of idiopathic hypersomnia
Orphan Designation Status:	Designated
FDA Orphan Approval Status:	Not FDA Approved for Orphan Indication
Sponsor:	Jazz Pharmaceuticals Ireland Limited 5th Floor Waterloo Exchange Waterloo Road Dublin Ireland *The sponsor address listed is the last reported by the sponsor to OOPD.*

*Exclusivity Protected Indications are shown for approvals from Jan. 1, 2013, to the present.

Note that Xyrem's designation for IH is listed under its generic chemical synonym, gamma-hydroxybutyric acid. Orphan drug designation is given to an "active moiety", not a single small molecule, so that the designated orphan drug actually includes a set of closely related chemicals that include the various salts of the base molecule, which in this case is gamma-hydroxybutyric acid.

"Gamma-hydroxybutyric acid", "sodium oxybate", "Xyrem", and any other chemical names and drug formulations that employ gamma-hydroxybutyric acid as the active moiety are considered equivalent for the purposes of orphan drug designation under Federal Regulations (unless a new formulation is specifically shown to be clinically superior from the originally designated drug). The relevant passages read:

> (2) Active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

And:

> (14) *Same drug* means:
>
> (i) If it is a drug composed of small molecules, a drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug, even if the particular ester or salt (including a salt with hydrogen or coordination bonds) or other noncovalent derivative such as a complex, chelate or clathrate has not been previously approved, except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.

(Orphan Drugs Rule, 21 C.F.R. §316.3, 2020)

Anthem's Denial Is Based on Invalidated and Irrelevant Criteria

Executive Summary

> There is no pathognomonic sign or symptom that is diagnostic of IH.
>
> (Saini, Prabhjyot, and David B. Rye. 2017. "Hypersomnia: Evaluation, Treatment, and Social and Economic Aspects." *Sleep Medicine Clinics* 12(1): 47–60.)
>
> The MSLT is the least discriminating test of daytime sleepiness.
>
> (Johns, Murray W. 2000. "Sensitivity and Specificity of the Multiple Sleep Latency Test (MSLT), the Maintenance of Wakefulness Test and the Epworth Sleepiness Scale: Failure of the MSLT as a Gold Standard." *Journal of Sleep Research* 9(1): 5–11.)

The basis on which Anthem separates patients into “narcolepsy” patients, who may be approved for Xyrem, and “idiopathic hypersomnia” patients, who may be denied, is the appearance of multiple sleep onset REM periods on the MSLT.

However, the SOREM test is extremely unreliable for making this categorization. It is also irrelevant to clinical management of the patient.

In the following sections I will demonstrate in further detail that:

1. Multiple SOREMs cannot reliably categorize patients into the categories NT2 and IH. The categorization is little better than chance.
2. Categories based on SOREMs are irrelevant to treatment, by both evidence and logic.
3. Multiple SOREMs are not an accurate biomarker for narcolepsy and have no meaning on an individual MSLT.

The following sections will show how the SOREM test and the MSLT have been proven by multiple studies to be unreliable for sorting any given patient into NT2 and IH. In the largest study to date, they perform little better than chance. SOREMs are so poor a marker for narcolepsy that they do not even perform very well for diagnosing NT1. SOREMs are an invalidated, arbitrary basis on which to deny care.

In fact, there is no set of symptoms or tests that can separate IH and NT2 reliably, there is no substantial knowledge of the etiology or pathophysiology of either entity, and multiple authors have made the obvious suggestion that they may not be separate disease entities at all.

Certainly there is no basis on which to treat them as separate for clinical management. There is no evidence that any drugs used to treat narcolepsy have a different effect in idiopathic hypersomnia—and there is no plausible reason they *would*. All drugs tested work the same without regard for SOREMs, because SOREMs are not a meaningful marker for any pathology specific to narcolepsy. SOREMs are an irrelevant basis on which to deny care.

In other words, an idiopathic hypersomnia diagnosis is a narcolepsy diagnosis, by any and all measures that matter clinically. I know Anthem would not want to deny me coverage for a necessary treatment based only on an invalidated and irrelevant “diagnostic” marker.

> We should consider the current findings as a wakeup call… Moreover, we might consider focusing more on tests that can separate sleep disorders from life style disorders, instead of trying to stick to unclear categories such as narcolepsy without cataplexy, which may only exist because of the existence of the MSLT.
>
> (Mayer, Geert, and Gert Jan Lammers. 2014. "The MSLT: More Objections than Benefits as a Diagnostic Gold Standard?" *Sleep* 37(6): 1027–28.)

Additionally, Anthem bases its Approval Criteria for renewing Xyrem on the ESS and MWT. As has been shown, at best, these tests are both simply measures of sleep propensity only. They do not measure any of the numerous other symptoms known to occur in patients with hypersomnias, including daytime sleepiness itself, brain fog, cognitive dysfunction, etc. Using only the ESS and MWT also fails to consider in any way the long-term consequences of disrupted sleep from these sleep disorders. In short, these tests are completely inadequate to measure improvements in hypersomnias.

The MSLT and SOREMs Do Not Reliably Categorize Patients Into IH or NT2

An accurate test should be reliable: it should give the same diagnosis to a given patient each time they take the test. Unfortunately, the only reliable thing about the MSLT is its incredibly poor performance. The SOREM criteria used on the MSLT to separate NT2 and IH are particularly unreliable.

There is widespread agreement in the scientific community that this test is unacceptable for making a diagnostic distinction between NT2 and IH.

The odds the test will yield the same results on repeat testing have been shown to be little better than chance. Surely Anthem would not deny my care based on the outcome of a coin flip.

> The continued use of SOREMs to distinguish narcolepsy without cataplexy from idiopathic hypersomnia is not justified.
>
> The distinction between narcolepsy without cataplexy and idiopathic hypersomnia based on MSLT testing alone does not appear justified.
>
> It is possible that idiopathic hypersomnia and narcolepsy without cataplexy are manifestations of the same underlying pathology or exist along a spectrum with overlapping features. Family studies of narcolepsy (with and without cataplexy) support this assertion, as family members of narcoleptics have higher rates of

narcolepsy, but also of idiopathic hypersomnia, excessive daytime sleepiness, and abnormal multiple sleep latency tests.

(Trotti, Lynn Marie, Beth A. Staab, and David B. Rye. 2013. “Test-Retest Reliability of the Multiple Sleep Latency Test in Narcolepsy without Cataplexy and Idiopathic Hypersomnia.” Journal of Clinical Sleep Medicine 09(08): 789–95.)

The presented results suggest that a positive MSLT is not a trait marker of narcolepsy without cataplexy… What is the value of performing an MSLT in subjects without cataplexy when only 10% to 20% of those who have a positive initial MSLT show it four years later, as in this study?

(Mayer, Geert, and Gert Jan Lammers. 2014. “The MSLT: More Objections than Benefits as a Diagnostic Gold Standard?” *Sleep* 37(6): 1027–28.)

This finding is mirrored in the general population, in which the finding of multiple SOREMs has a kappa of only 0.1, that is, repeatability is only minimally higher than expected by chance alone.

(Trotti, Lynn Marie. 2017. “Idiopathic Hypersomnia.” Sleep Medicine Clinics 12(3): 331–44.) referring to

The concordance for a positive MSLT [in NT2] was quite low and not significantly different than controls.

[NT2 and IH] are essentially diagnoses of exclusion that have relied upon a test prior to completion of proper validation studies. Diagnoses are therefore frequently rendered without regard to accumulating evidence that… test-retest reliability of the MSLT outside the context of NT1 appears poor.

A single positive MSLT as defined by ICSD-3 has little diagnostic value as currently defined…The continued use of the MSLT as per ICSD-3 to differentiate NT2 from IH should be reevaluated.

(Ruoff, Chad et al. 2018. “The MSLT Is Repeatable in Narcolepsy Type 1 But Not Narcolepsy Type 2: A Retrospective Patient Study.” *Journal of Clinical Sleep Medicine* 14(01): 65–74.)

The PSG–MSLT measures and classification are not stable in patients with noncataplectic central disorders of hypersomnolence, with frequent diagnostic changes, particularly for NT2 and IH.

(Lopez, Régis et al. 2017. “Test–Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence.” *Sleep* 40(12).)

> The MSLT was developed and validated as an aid in the diagnosis of narcolepsy [with cataplexy], and since then it has been shown to possess significant flaws of accuracy and precision….
>
> Test-retest reliability outside of the context of NT1 appears poor.
>
> (Saini, Prabhjyot, and David B. Rye. 2017. "Hypersomnia: Evaluation, Treatment, and Social and Economic Aspects." *Sleep Medicine Clinics* 12(1): 47–60.)

> These weaknesses result in low test-retest reliability of the MSLT.
>
> (Baumann, Christian R. et al. 2014. "Challenges in Diagnosing Narcolepsy without Cataplexy: A Consensus Statement." *Sleep* 37(6): 1035–42.)

> The lesson learned about the MSLT… is that we cannot continue to rely on 'sleepability' as our most fundamental measure of the complex and multifaceted experience of hypersomnolence.
>
> (Trotti, Lynn Marie. 2016. "Another Strike Against Sleepability." *Journal of Clinical Sleep Medicine* 12(04): 467–68.)

> These results challenge generally accepted knowledge regarding the prevalence of narcolepsy without cataplexy and MSLT SOREMPs. Our results suggest… the need for re-evaluating the MSLT as a diagnostic tool for narcolepsy.
>
> (Mignot, Emmanuel et al. 2006. "Correlates of Sleep-Onset REM Periods during the Multiple Sleep Latency Test in Community Adults." *Brain* 129(6): 1609–23.)

> Mindful that the sensitivity and specificity of the MSLT is low for IH and narcolepsy type 2, we should allow a different approach in future classifications for patients who have genuine complaints of hypersomnolence but fail to have diagnostic MSLT results.
>
> (Lammers, Gert Jan et al. 2020. "Diagnosis of Central Disorders of Hypersomnolence: A Reappraisal by European Experts." *Sleep Medicine Reviews* 52: 101306.)

Specific Findings

Goldbart, Aviv et al. 2014. "Narcolepsy and Predictors of Positive MSLTs in the Wisconsin Sleep Cohort." *Sleep* 37(6): 1043–51.

Note: the Kappa coefficient (κ) is a measurement of reliability that accounts for the possibility of agreement by chance. In biomedicine, a κ between 0-0.2 should be interpreted as "no agreement", with 0-4% of the data being reliable (McHugh 2012).

- A population-based longitudinal study, with PSG-MSLT repeated in 590 adults.
- After controlling for age, sex, shift work, short sleep, and sleep apnea:
    - κ = 0.1 for having ≥2 SOREMs on the MSLT (i.e., no agreement between tests)
    - κ = 0.1 for having a positive MSLT (again, no agreement between tests)

Ruoff, Chad et al. 2018. "The MSLT Is Repeatable in Narcolepsy Type 1 But Not Narcolepsy Type 2: A Retrospective Patient Study." *Journal of Clinical Sleep Medicine* 14(01): 65–74.

- Multi-center retrospective study of patients with at least 2 clinical MSLTs where at least one was positive for NT2 (n=54)
    - 83% of cases changed diagnosis on repeat MSLT testing
        - 30% changed SOREM category (between multiple or non-multiple SOREMs)
    - 70% of NT2 cases had one MSLT with <2 SOREMs
        - MSLT concordance for NT2 (NT2 on both tests) was 17%
        - 26% of NT2 cases also had a positive test for IH (14 of 54)
- Normal controls with at least 2 MSLTs were drawn from the Wisconsin Sleep Cohort for comparison. To adjust for differences in selection bias between the disease and control groups, only the subset with positive results on the first MSLT was examined (In NT2, n=30, In controls, n=13). Multivariate analyses also controlled for age, sex, and medication status.
    - Adjusted MSLT repeatability for NT2 in this subset was still only 30%.
    - Repeatability was not significantly different for NT2 cases versus controls.

Lopez, Régis et al. 2017. "Test–Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence." Sleep 40(12).

- Multi-center retrospective study of patients with a primary hypersomnolence complaint, without cataplexy, who had at least two clinical MSLT under drug-free conditions (n = 75).
- 61% of patients changed diagnosis on repeat MSLT testing

    - 33% changed SOREM category (between multiple or non-multiple SOREMs)
- 50% of NT2 cases also had one MLST with <2 SOREMs (14 of 28)
    - MSLT concordance for NT2 (NT2 on both tests) was 29% (8 of 28 NT2 positive tests)
    - MSLT concordance for IH (IH on both tests) was 17% (5 of 29 IH positive tests)
- 18% of NT2 cases also had a positive test for IH (5 of 28)

Trotti, Lynn Marie, Beth A. Staab, and David B. Rye. 2013. "Test-Retest Reliability of the Multiple Sleep Latency Test in Narcolepsy without Cataplexy and Idiopathic Hypersomnia." Journal of Clinical Sleep Medicine 09(08): 789–95.

- Multi-center retrospective study of patients with a primary hypersomnolence complaint, without cataplexy, who had at least two clinical MSLT (n = 36).
- 53% of patients changed diagnosis on MSLT retesting
    - 31% changed SOREM category (multiple or non-multiple SOREMs)
- 47% of NT2 cases had one MLST with <2 SOREMs (8 of 17)
    - MSLT concordance for NT2 (NT2 on both tests) was 29% (5 of 17 NT2 diagnoses)
    - MSLT concordance for IH (IH on both tests) was 42% (8 of 19 IH diagnoses)
- 14% of patients diagnosed with NT2 or IH shifted between those diagnoses

Huang, Yu-Shu et al. 2018. "Multiple Sleep Latency Test in Narcolepsy Type 1 and Narcolepsy Type 2: A 5-Year Follow-up Study." *Journal of Sleep Research* 27(5): e12700.

- 46 teenagers and young adults diagnosed with NT2 in Taiwan repeated the MSLT every year for five years.
- 24% had <2 SOREMPs on at least one MSLT.
    - 11% had <2 SOREMPs on *multiple* MSLTs.

SOREMs Are Clinically Irrelevant for Treatment

There is no evidence or even a plausible basis for clinically-significant differences between narcolepsy and IH for any drug therapy. Instead, all drugs tested so far have shown similar performance across narcolepsy and IH, including Xyrem. This is unsurprising given that IH and NT2 are diagnostically indistinguishable.

> There is no evidence that the pathophysiology or therapeutic response is substantially different for hypersomnia with or without SOREMPs on the MSLT.
>
> (Mignot, Emmanuel J.M. 2012. “A Practical Guide to the Therapy of Narcolepsy and Hypersomnia Syndromes.” Neurotherapeutics 9(4): 739–52.)

> [Poor sensitivity and specificity] and the absence of apparent therapeutic or biological significance to multiple SOREMs argue that the continued use of SOREMs to distinguish narcolepsy without cataplexy from idiopathic hypersomnia is not justified.
>
> (Trotti, Lynn Marie, Beth A. Staab, and David B. Rye. 2013. “Test-Retest Reliability of the Multiple Sleep Latency Test in Narcolepsy without Cataplexy and Idiopathic Hypersomnia.” Journal of Clinical Sleep Medicine 09(08): 789–95.)

There is literally not a single drug that has shown efficacy for sleepiness in narcolepsy that has not also been effective when tested for IH.

Direct comparisons of treatment responses between IH patients and narcolepsy patients have all shown modafinil, mazindol, and Xyrem have similar benefits and risks in both groups:

> [Xyrem] improved daytime sleepiness [in IH] to the same degree as in patients with narcolepsy type 1. This improvement was observed despite the fact that SXB was used at a lower dose in IH than in NT1 and after patients had tried other stimulants.
>
> (Leu-Semenescu, Smaranda, Pauline Louis, and Isabelle Arnulf. 2016. “Benefits and Risk of Sodium Oxybate in Idiopathic Hypersomnia versus Narcolepsy Type 1: A Chart Review.” *Sleep Medicine* 17: 38–44.)

> Modafinil produced a similar ESS change in IH patients and in narcolepsy patients and a similar benefit as estimated by the patients and clinicians.
>
> (Lavault, Sophie et al. 2011. “Benefit and Risk of Modafinil in Idiopathic Hypersomnia vs. Narcolepsy with Cataplexy.” *Sleep Medicine* 12(6): 550–56.)

> The benefit of mazindol on sleepiness… was important and similar in both groups.
>
> (Nittur, Nandini et al. 2013. “Mazindol in Narcolepsy and Idiopathic and Symptomatic Hypersomnia Refractory to Stimulants: A Long-Term Chart Review.” *Sleep Medicine* 14(1): 30–36.)

In addition, studies of modafinil and pitolisant conducted in IH patients alone have yielded similar benefits and side effect profiles as recorded for IH and narcolepsy elsewhere (Leu-Semenescu et al. 2014; Mayer et al. 2015). Additional drugs, particularly the various amphetamines, lack formal publications for IH, but have a very long clinical history of use in both groups.

SOREMs Are Not Specific or Sensitive Even in NT1

When the MSLT was designed in the 1970s, multiple SOREMs were thought to be pathognomonic for narcolepsy—a highly *specific* marker that was only observed in narcolepsy, and a highly *sensitive* marker that was observed in nearly all cases of narcolepsy. It is on this basis that the SOREM criteria were created.

We now know neither is the case.

First, the presence of multiple SOREMs does not indicate the presence of narcolepsy. Multiple SOREMs occur on MSLTs of 4-7% of normal adults and much more frequently in many sleep-disordered conditions (Goldbart et al. 2014; E. Mignot et al. 2006; Singh, Drake, and Roth 2006).

Second, the absence of multiple SOREMs does not indicate the absence of narcolepsy. SOREMs frequently fail to occur as expected on the MSLTs of narcoleptics. This should be abundantly clear from the data on NT2 presented already, but it is also true for NT1, as I will show below.

Why am I bothering to explain this about NT1? Because it further demonstrates how extraordinarily badly the MSLT fails at detecting narcolepsy of any kind, and how utterly meaningless the presence or absence of SOREMs is to narcolepsy for any individual MSLT.

Allen notes that the SOREM test for narcolepsy is so bad that as a single predictor, it is actually more likely to be wrong than right, and even more so in women than for men:

> [Multiple SOREMs] occur in 13% of males and 6% of females, making it only somewhat more specific for narcolepsy than is average MSLT ≤ 8 min."
>
> This lack of specificity is particularly important for a test to diagnose an uncommon disorder since it translates into very poor positive predictive value for the diagnosis. For example, in this study more than half of the males and 80% of the females with

> two SOREMs had an average MSLT > 8 min; that is, the SOREM test alone is more likely to be false than true for the diagnosis of narcolepsy, particularly for females.
>
> (Allen, Richard P. 2006. "When, If Ever, Can We Use REM-Onset Naps on the MSLT for the Diagnosis of Narcolepsy?")

In the absence of a spinal tap or visible cataplexy, SOREM-lacking people with narcolepsy type 1 will be diagnosed with IH and/or NT2, like myself. The best estimates indicate that around 10-20% cases of NT1 go undiagnosed on the MSLT, mostly due to the SOREM criteria, even though this is the patient group for which the MSLT is the most reliable. The false negative rate for NT2, which can't be directly measured, can be assumed to be at least this high, but is likely much, much higher.

Unlike NT2 or IH, NT1 has two laboratory tests considered "gold-standard" diagnostics to which we can compare the MSLT: orexin deficiency in the cerebrospinal fluid or the presence of the high-risk allele (HLA)–DQB1*06:02 plus confirmed cataplexy. In "gold standard" NT1 patients, the MSLT fails 7-21% of the time, usually because of SOREM failures.

- In the largest study to date, the MSLT was falsely negative in 9.7% of 1099 gold-standard NT1 cases in the European Narcolepsy Network database. This was almost always because of the SOREM criteria: 9.6% of NT1 cases had fewer than the "required" 2 SOREMs on the MSLT, with 3.9% having none at all. (Luca, Gianina et al. 2013. "Clinical, Polysomnographic and Genome-Wide Association Analyses of Narcolepsy with Cataplexy: A European Narcolepsy Network Study." *Journal of Sleep Research* 22(5): 482–95.)

This is in line with the false negative rates in other smaller "gold standard" based studies:

- Gabryelska et al. found the MSLT was falsely negative in 21% of 19 gold-standard NT1 patients. SOREM criteria failed in 10.5%. (Gabryelska, Agata et al. 2020. "Utility of Measuring CSF Hypocretin-1 Level in Patients with Suspected Narcolepsy." *Sleep Medicine* 71: 48–51.)

- Mignot et al. found the MSLT was falsely negative in 14% of 90 gold-standard NT1. SOREM criteria failed in all of these cases (14%).

(Mignot, Emmanuel et al. 2002. “The Role of Cerebrospinal Fluid Hypocretin Measurement in the Diagnosis of Narcolepsy and Other Hypersomnias.” *Archives of Neurology* 59(10): 1553–62.)

- Lopez et al found the MSLT was falsely negative in 27% of 22 gold-standard NT1 patients. SOREM criteria failed in 5%.
  (Lopez, Régis et al. 2017. “Test–Retest Reliability of the Multiple Sleep Latency Test in Central Disorders of Hypersomnolence.” *Sleep* 40(12).)

- Andlauer et al. found the MSLT was falsely negative in 7.1% of 516 gold-standard NT1 patients. The number due to SOREM failure was not broken out in this study, but it was mentioned explicitly as occurring.
  (Andlauer, Olivier et al. 2013. “Nocturnal Rapid Eye Movement Sleep Latency for Identifying Patients with Narcolepsy/Hypocretin Deficiency.” *JAMA Neurology* 70(7): 891–902.)

Studies still reach similar estimates for the false negative rates of the MSLT and SOREM criteria when using slightly less stringent criteria for the NT1 “gold standard”, such as confirmed cataplexy plus abnormal scores on the Epworth Sleepiness Scale:

- Aldrich et al. found the MSLT failed in 29% of 106 NT1 patients. SOREM criteria failed in 26%, with 13% displaying no SOREMs at all.
  (Aldrich, Michael S., Ronald D. Chervin, and Beth A. Malow. 1997. “Value of the Multiple Sleep Latency Test (MSLT) for the Diagnosis of Narcolepsy.” *Sleep* 20(8): 620–29.)

Studies of test-retest reliability for NT1, with patients taking the MSLT twice, also confirm similar false negative rates:

- Lopez et al found the MSLTs failed in 19% in 16 NT1 cases. SOREM criteria failed in 6%.
  (Lopez, Régis et al. 2017.)

- Ruoff et al. found the MSLTs failed in 28% of 60 NT1 cases. SOREM criteria failed in 23%
  (Ruoff, Chad et al. 2018.)

Allen supplies the inescapable community-wide conclusion with an almost humorous understatement:

> Overall the results are not very supportive of SOREMs as a specific test for narcolepsy….
>
> Massive under-diagnosis certainly seems possible.
>
> (Allen, Richard P. 2006.)

SOREM Criteria Discriminate Based on Sex, Age, and Medication Status

Executive Summary

Using SOREMs as the sole diagnostic criteria to separate patients into NT2 and IH isn't simply arbitrary: it is also discriminatory. Certain groups of people are far more likely to experience SOREMs, *independent* of narcolepsy.

Here, I will show that SOREM criteria are biased based on sex, age, and medication status. This makes SOREMs an inherently discriminatory method of diagnosis—and thus an inherently discriminatory barrier to effective care for women, older adults, and patients who rely on REM-suppressing medications.

This section provides a summary. The sections that follow provide the evidence base from the scientific literature.

SOREM frequency is inherently age- and sex-dependent, across healthy people as well as sleep disordered populations. Older adults and women are each dramatically less likely to experience SOREMs on the MSLT due to intrinsically lower REM-propensity with age and with female sex, unrelated to narcolepsy pathology.

Similarly, patients who rely on REM-suppressing medications obviously have a lower REM propensity than patients who are not using such medications. They are less likely to display SOREMs, for reasons that are unavoidable for practical purposes.

Many common neurological medications are REM-suppressing, such as SSRI and SNRI antidepressants. It is unreasonable and irresponsible to expect patients with disorders like depression, anxiety, bipolar disorder, chronic pain, or epilepsy to risk

dangerous and painful relapses by discontinuing their medication for weeks prior to the MSLT.

Furthermore, if they were to relapse, many of these patients would become ineligible for *any* primary hypersomnia diagnosis: a positive MSLT during such a relapse would be considered invalid. The ICSD-3 diagnostic criteria for primary hypersomnias require first ruling out other possible causes of sleepiness, like uncontrolled depression or epilepsy. With both the original disorder and the treatment as potential confounding factors, the SOREM criteria arbitrarily reduce the chance these patients will receive a narcolepsy diagnosis, *no matter what they chose to do*.

Despite this knowledge, the diagnostic criteria for narcolepsy and IH are not adjusted for age, sex, or medication status. Anthem also does not adjust for age, sex, or medication status in their Xyrem Approval Criteria, to compensate for this bias in the diagnostic criteria. This means that women, older adults, and patients reliant on REM-suppressing medication are more likely to be denied coverage for Xyrem, based on a measure inherent to these population groups, not a measure inherent in their actual disease pathology, symptoms, clinical needs, or clinical response to Xyrem.

I am a member of two of these three groups unfairly disadvantaged by SOREM criteria:

- I am a woman.
- I was 32 when I had my sleep studies—well past the mean for adult SOREM propensity. If I were to retake the test now, my chance of exhibiting SOREMs would be even lower.

My odds of being diagnosed with narcolepsy rather than idiopathic hypersomnia were reduced many times over for reasons utterly unrelated to disease pathology.

Surely Anthem does not want to deny women, older adults, and patients with depression equal access to effective treatments, based solely on criteria that the published scientific literature has criticized and rejected so thoroughly. I request that Anthem adjust appropriately for my sex and age at diagnosis and approve my treatment with Xyrem without regard to SOREMs.

Age: The MSLT Discriminates Based on Age

Reduced incidence of SOREMs is an intrinsic feature of age, across both healthy and sleep-disordered populations. Across both healthy and sleep-disordered populations, age has been confirmed as a highly predictive and highly significant variable for SOREMs. Incidence of SOREMs appears to decrease beginning in the late 20s.

This means that the later in adulthood that patients are tested, the less likely they are to be diagnosed with narcolepsy and more likely to be diagnosed with IH--not because narcolepsy magically disappears with age, but because older adults intrinsically have fewer SOREMs than younger adults.

> The progressive decrease in the number of SOREMP and increase in the mean sleep latency on the MSLT as a function of age suggest that the current criteria used for diagnosis may be too stringent in older patients. The major influence of age on MSLT results should therefore be taken into account when diagnosing a narcoleptic patient.
>
> (Dauvilliers, Y. et al. 2004. "Effect of Age on MSLT Results in Patients with Narcolepsy-Cataplexy." *Neurology* 62(1): 46–50.)

> [Our study] highlights the reduced sensitivity of the MSLT in detecting narcolepsy in older individuals. This conclusion is based on the growing literature substantiating age-related decline in nocturnal and diurnal REM amount.
>
> (Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. "Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance." *Sleep Medicine* 55: 115–23.)

> Age-related changes in MSLT outcomes, including a decrease in the number of SOREMPs and increase in the mean sleep latency with increasing age, as well as poor reliability and lack of adequate normative data in children and adolescents, reduce interpretability of the MSLT.
>
> (Ruoff, Chad, and David Rye. 2016. "The ICSD-3 and DSM-5 Guidelines for Diagnosing Narcolepsy: Clinical Relevance and Practicality." *Current Medical Research and Opinion* 32(10): 1611–22.)

Findings in General or Healthy Populations:

Goldbart, Aviv et al. 2014. "Narcolepsy and Predictors of Positive MSLTs in the Wisconsin Sleep Cohort." *Sleep* 37(6): 1043–51.

- Population-based longitudinal study

- 1,135 randomly-invited subjects completing at least 1 PSG-MSLT
- Strongly confirmed prevalence of multiple SOREMs decreases with age, with variable significance of p = 0.005

Findings in Hypersomnolent Patients:

Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. "Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance." Sleep Medicine 55: 115–23.

- Multi-center retrospective analysis of 2,498 cases evaluated for hypersomnolence.
- Age was a strong predictor for SOREMs frequency, with older age correlated to fewer SOREMs.
- Patients over the age of 21, compared to patients age 13-21, had less chance of displaying any SOREMs on the MSLT overall, and for each nap individually. See Figures 2 and 3.

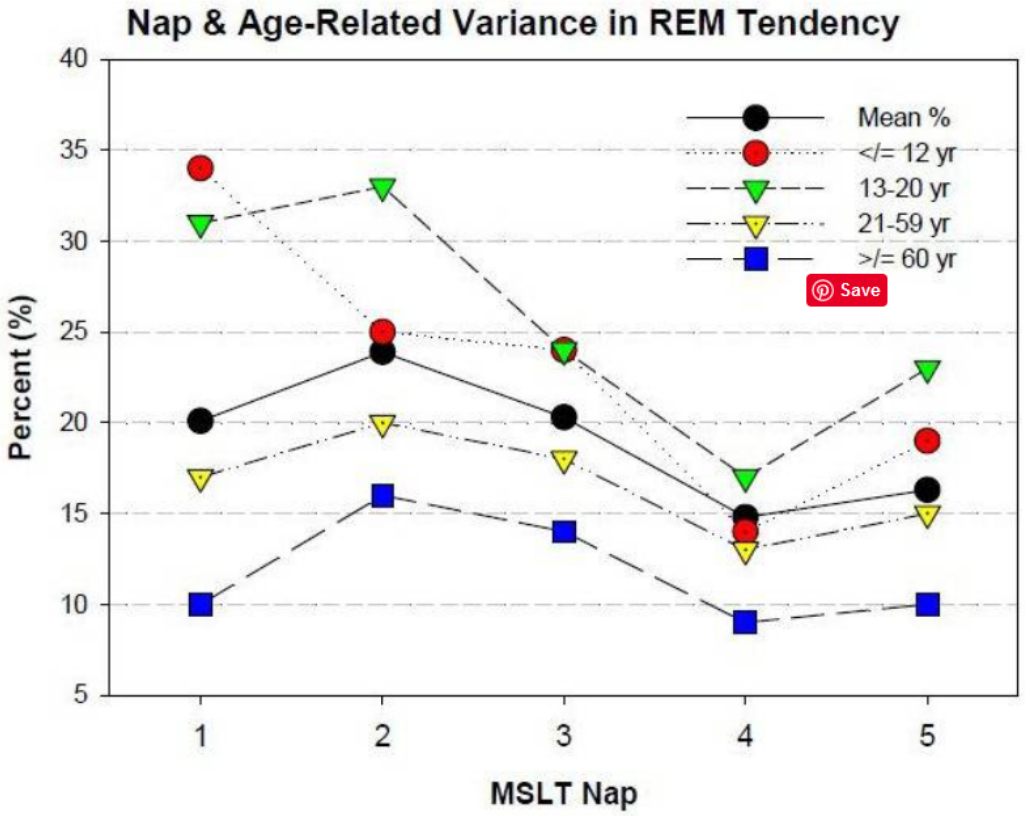

Figure 2: Nap and Age-Related Variance in SOREM (from Cairns et al.)

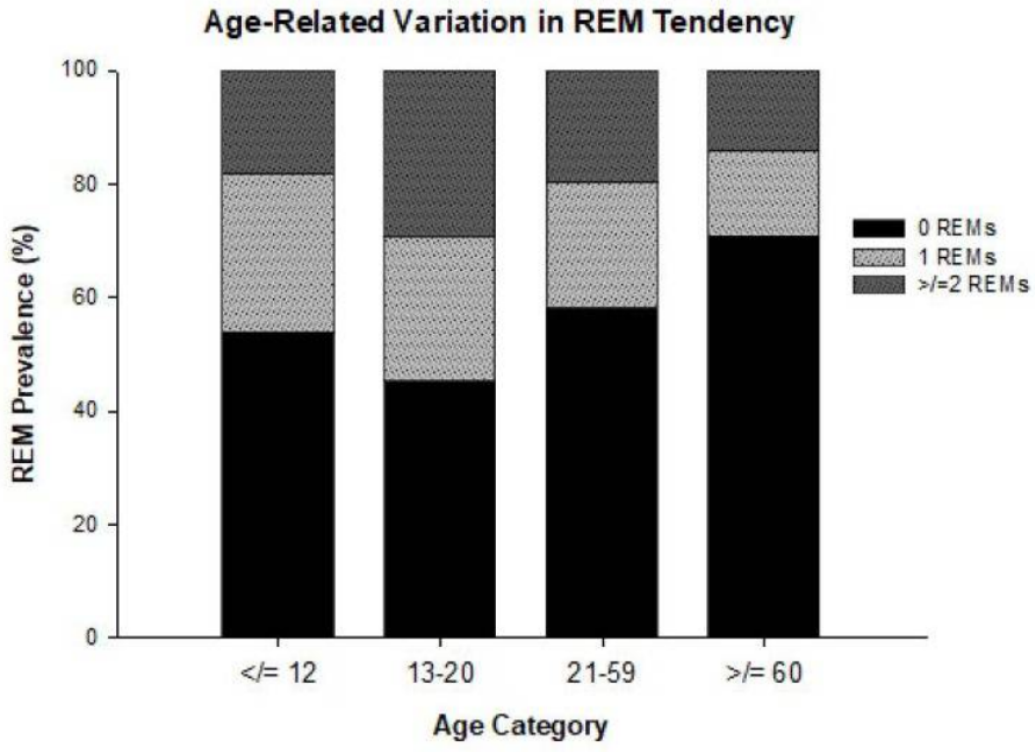

Figure 3: Age-Related Variation in SOREM (from Cairns et al)

Sansa, Gemma et al. 2014. "Non-Random Temporal Distribution of Sleep Onset REM Periods in the MSLT in Narcolepsy." Journal of the Neurological Sciences 341(1–2): 136–38.

- Single-center study of PSG-MSLTs from 129 patients with NT1 or NT2.
- Patients older than 29 years had fewer SOREMs than patients age 11-28 (p 0.045).

Sex: The MSLT Discriminates Against Women

Men display more SOREMs than women, across healthy and sleep-disordered populations. This is one of the strongest predictors of SOREMs, and is understood to be due to an intrinsic sex-based difference in REM sleep regulation.

Thus, men are more likely than women to receive narcolepsy diagnoses because of differences in SOREM propensity that are sex-based, not narcolepsy-based. Men are thus more likely than women to be authorized for Xyrem and other "narcolepsy-only" drugs from Anthem, simply because they are *male*. By the same effect, women like me are more likely to receive an idiopathic hypersomnia diagnosis instead, and thus less likely to be covered for the same range of effective therapies as hypersomnolent men.

Findings in General or Healthy Populations:

Goldbart, Aviv et al. 2014. "Narcolepsy and Predictors of Positive MSLTs in the Wisconsin Sleep Cohort." *Sleep* 37(6): 1043–51.

- Population-based longitudinal study
- 1,135 randomly-invited subjects completing at least 1 PSG-MSLT
- Strongly confirmed prevalence of multiple SOREMs decreases with age
- Men were nearly 3 times more likely than women to have multiple SOREMs on the MSLT controlled for age, shift work, and short sleep (OR 2.75, p = < 0.0001)

These results confirmed earlier smaller samples from this cohort. The authors at that time concluded:

> The occurrence of SOREM is strongly sex-dependent.
>
> None of the parameters found to be significant in males with SOREM predicted SOREMs in females, suggesting fundamental differences in REM sleep regulation between the sexes.
>
> (Mignot, Emmanuel et al. 2006. "Correlates of Sleep-Onset REM Periods during the Multiple Sleep Latency Test in Community Adults." *Brain* 129(6): 1609–23.)

Bishop, Christopher et al. 1996. "The Frequency of Multiple Sleep Onset REM Periods among Subjects with No Excessive Daytime Sleepiness." Sleep 19(9): 727–30.

- Single-center study of PSG-MSLTs in 139 healthy, drug-free volunteers.
- PSG (polysomnography) indicated no sleep apnea and adequate TST (total sleep time).
- Men were 3 times as likely as women to display multiple SOREMPs.

Findings in Sleep Apnea Patients:

Chervin, Ronald D., and Michael S. Aldrich. 2000. "Sleep Onset REM Periods during Multiple Sleep Latency Tests in Patients Evaluated for Sleep Apnea." *American Journal of Respiratory and Critical Care Medicine* 161(2 I): 426–31.

- Single-center retrospective analysis of PSG-MSLTs of 1,145 patients evaluated for suspected sleep apnea and not suspected of central hypersomnias, and free from psychoactive drugs
- Men were nearly 4.4 times more likely than women to have multiple SOREMs on the MSLT, in a study of patients with sleep apnea (OR 4.380, p = 0.0002)

- This difference was not related severity or frequency of apnea events or REM pressure as shown on PSG
- Male sex was the strongest predictor of having ≥2 SOREMs out of any predictive variables

Findings in Hypersomnolent Patients:

Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. "Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance." *Sleep Medicine* 55: 115–23.

- Multicenter retrospective analysis of PSG-MSLTs of 2,498 patients evaluated for suspected hypersomnias.
- The largest database of clinical PSG-MSLTs published to date.
- Men were 1.5 times more likely than women to have multiple SOREMs on the MSLT (OR: 1.49).
- Women and men were equally likely to meet the diagnostic threshold for sleep latency.
- This allowed men to qualify for a narcolepsy diagnosis about 1.5 times more often than women (OR: 1.55), while women were more likely to get an IH diagnosis instead (Male OR: 0.58).
- Results were controlled for age, race, and the use of REM-suppressing medications.

The authors concluded:

> Because the diagnostic criteria for NT2 and IH differ only in number of MSLT SOREMPs, an underlying gender difference in REM propensity would tend to systematically increase the percentage of sleepy women, relative to men, diagnosed with idiopathic hypersomnia.

Medication Status: The MSLT Discriminates Against People Who Require REM-Suppressing Medications

REM-suppressing medications have been shown to reduce SOREMs in multiple large studies, in the general population as well as sleep-disordered patients. See findings subsections below.

Sleepy patients who rely on REM-suppressing medication have two choices on their MSLT: bad and worse. Do they keep the psychiatric disorder under stable control but

accept a greatly reduced chance of a narcolepsy diagnosis and medication access? Or do they risk a (dangerous, painful) relapse that may actually prevent a receiving sleep diagnosis *at all*?

> Despite the recommendation that patients should 'ideally' stop REM suppressants for at least two weeks prior to testing, only 5.9% of patients taking ≥1 REM suppressant agent suggested that they refrained from said compound(s) prior to the MSLT.
>
> (Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. "Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance." *Sleep Medicine* 55: 115–23.)

Even if patients are instructed to withdraw from their medication, it is unclear when they would need to do so in order to have "valid" results. Timeframes for withdrawal are not standardized, let alone tested and validated.

> There is also a lack of consensus on how long a patient should be free from psychoactive medications, most of which suppress REM sleep, before performing a PSG followed by MSLT. Moreover, in some clinical situations, it may not even be clinically feasible that medications be discontinued (e.g., antidepressant therapy).
>
> (Ruoff, Chad, and David Rye. 2016. "The ICSD-3 and DSM-5 Guidelines for Diagnosing Narcolepsy: Clinical Relevance and Practicality." *Current Medical Research and Opinion* 32(10): 1611–22.)

> Medications such as antidepressants or other psychotropic drugs may significantly affect REM sleep for weeks or months after discontinuation, but management of these medications is not uniformly defined for MSLT protocols.
>
> (Baumann, Christian R. et al. 2014. "Challenges in Diagnosing Narcolepsy without Cataplexy: A Consensus Statement." *Sleep* 37(6): 1035–42.)

Despite widespread understanding that patients on REM-suppressing medications are unlikely to display SOREMs, Anthem has made no adjustment to the diagnostic interpretation for medication status nor any compensation for it in their Xyrem Approval criteria. Although this particular bias is not present in my case, it underscores yet another reason that Anthem's current criteria are inadequate and systematically biased.

Findings in General or Healthy Populations:

> "For REM suppressant antidepressants such as SSRI, decreased antidepressant intake was observed in volunteers with SOREMPs."
>
> (Mignot, Emmanuel et al. 2006.)

Findings in Hypersomnolent Patients:

Kolla, Bhanu Prakash et al. 2020. "Advance Taper of Antidepressants Prior to Multiple Sleep Latency Testing Increases the Number of Sleep-Onset Rapid Eye Movement Periods and Reduces Mean Sleep Latency." *Journal of Clinical Sleep Medicine*.

- Single-center study of PSG-MSLTs from 502 patients with suspected primary hypersomnolence, with 178 taking REM-suppressing antidepressants.
- Patients who tapered off their antidepressant before the MSLT were more than 12 times as likely to have ≥2 SOREMs compared to patients still taking their antidepressants during the MSLT (OR=12.20).
- They were also more than 2 times as likely to have ≥2 SOREMs compared to patients who simply did not take antidepressants at all (OR=2.22), as well as shorter sleep latencies ($p>0.009$).
- Regression analysis controlled for multiple confounders.

Cairns, Alyssa, Lynn Marie Trotti, and Richard Bogan. 2019. "Demographic and Nap-Related Variance of the MSLT: Results from 2,498 Suspected Hypersomnia Patients: Clinical MSLT Variance." Sleep Medicine 55: 115–23.

- Multi-center retrospective analysis of 2,498 cases evaluated for hypersomnolence
- REM-suppressant use was associated with reduced odds of ≥2 REMs (OR: 0.52, $p<0.001$)
- And also reduced odds of MSLTs consistent with narcolepsy (OR: 0.60, $p=0.008$)
- Results were controlled for age, gender, and race

The authors concluded:

> We have now demonstrated a substantial association between REM suppressant use (specifically antidepressants and antipsychotics) and reduced MSLT SOREMPs/MSLT consistent with narcolepsy.

Conclusions

In conclusion, when considering this additional information for urgent/expedited appeal/external review, it behooves Anthem to consider:

1. I have a diagnosis of narcolepsy type 2 in addition to that of idiopathic hypersomnia, precisely because neither diagnostic nor clinical criteria can differentiate between them, and they are likely just two names for the same disorder.
2. The efficacy and medical necessity of Xyrem has been established in my personal case via improved symptoms and increased slow wave sleep.
3. Xyrem has been accepted as standard of care for over ten years for both IH and NT2 by the relevant medical community, with peer-reviewed evidence for the safety and efficacy of this treatment for cases like mine.
4. This standard of care is additionally reflected in prior precedents for coverage of Xyrem for idiopathic hypersomnia.
5. Coverage of Xyrem in my case is also considered medically necessary according to Anthem's own policy on off-label drugs.
6. Anthem has based its previous denials on criteria that I have demonstrated are:
    a. Unreliable for differentiating between NT2 and IH;
    b. Inadequate for determining symptomatic improvement;
    c. Unrelated to treatment efficacy; and
    d. Systematically discriminatory to patients like me who are women and diagnosed at an older age.

In this light, we can now reassess the claims made by Anthem in their denial letter: "The services are considered not medically necessary as defined in the definition section of your Certificate of Coverage (benefits booklet)." As I have clearly shown, Xyrem is medically necessary according to both Anthem's definition of medical necessity, its policies, and the standard of care.

> Your plan has re-reviewed your specific circumstances and health condition as documented in the grievance and medical records provided to us by your treating physician. The reviewer is a health plan Medical Director, an MD who is board certified and specializes in Internal Medicine. It's his recommendation that we keep our previous coverage decision. Here's why:
>
> We did not receive or did not see certain information about the use of the drug requested by your doctor, for your condition excessive daytime sleep (Idiopathic Hypersomnia). Use of this drug

> (XYREM 500 MG/ML SOLUTION) may be considered for approval under your health plan benefits when used for a certain condition (narcolepsy with or without cataplexy). We did not receive or we did not see information that shows you have this condition. We may consider approval of this drug for your condition under your health plan benefits if we receive certain information that show this drug can help your condition (medical literature references of medical studies of this drug for your condition or recognized drug compendia). We based this decision on your health plan prior authorization criteria for this drug and your health plan Off Label Drug Use policy, which can be found with other information on your prescription drug benefit at www.anthem.com/pharmacyinformation.

Clearly, no one at Anthem, including the anonymous reviewers re-reviewed (or ever initially reviewed) my "specific circumstances and health condition." Both my records and the letters from my doctor specifically indicate that I have a diagnosis of NT2 and that this diagnosis is indistinguishable from IH. Anthem has repeatedly confirmed receipt of this information, although the anonymous reviewers claim that "we did not receive or did not see certain information". Therefore, it can only be concluded that either my records and letters were not provided to the anonymous reviewers or that they completely ignored them. Certainly, they were not reviewed in any way.

Moreover, I have provided further extensive, compelling evidence that idiopathic hypersomnia is clinically indistinguishable from narcolepsy without cataplexy for the purposes of both diagnosis and treatment. This evidence from the literature only provides additional legitimacy to the efficacy that Xyrem has already demonstrated in my individual case.

"We may consider approval of this drug for your condition under your health plan benefits if we receive certain information that show this drug can help your condition (medical literature references of medical studies of this drug for your condition or recognized drug compendia)." Again, this information has been repeatedly provided and confirmed received by Anthem. Additionally, the medical literature, which I have provided in extensive and further detail in this document, clearly indicates that Xyrem is standard of care for both IH and NT2.

In fact, hundreds of articles support the use of Xyrem in numerous non-narcoleptic daytime sleepiness disorders, including idiopathic hypersomnia. These include retrospective and prospective studies demonstrating efficacy for excessive daytime sleepiness in at least four other diseases, including large randomized controlled clinical trials for Parkinson's disease and fibromyalgia. The fact that Xyrem has shown efficacy for excessive daytime sleepiness in multiple diseases which do not share NT1

pathophysiology indicates that its mechanism of action is not narcolepsy-dependent, and that its valid off-label uses are quite broad.

Although Anthem's denial letter states: "We based this decision on your health plan prior authorization criteria for this drug and your health plan Off Label Drug Use policy," my off-label drug use policy plainly requires coverage for individuals such as myself who are disabled by their chronic disease. Further, Anthem's Xyrem prior authorization criteria have been shown to be outdated and inadequate. They rely on references that are collectively irrelevant, outdated, incomplete, and unreliable. I have provided far more extensive, current, and comprehensive medical literature demonstrating that Xyrem is medically necessary for non-cataplectic hypersomnias. Once adjusted to be compatible with appropriate and current medical literature, I clearly meet criteria for Xyrem use.

I have shown that Xyrem significantly improves my severe disabling hypersomnia symptoms, that it does so more effectively than any of numerous other treatments I've tried, and it does so without side effects. Additionally and very importantly, Xyrem also reduces my risk for the diverse and serious long-term health consequences of disrupted sleep, such as Alzheimer's disease, heart attack, and colon cancer.

I hope this information has been helpful in demonstrating that Anthem has a clear prerogative to overturn the errors of their anonymous reviewers. I appreciate Anthem promptly reevaluating this case, and request that they act swiftly to approve my coverage for Xyrem.

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